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Gallium (III)-catalysed Bromocyanation of Alkynes: Regio- and Stereoselective Synthesis of β-Bromo-α,β-unsaturated Nitriles

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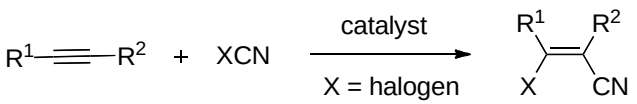
Treatment of arylacetylenes and cyanogen bromide in $ClCH_2CH_2Cl$ with a catalytic amount of $GaCl_3$ afforded (*Z*)-β-bromoacrylonitriles with high regio- and stereoselectivity.

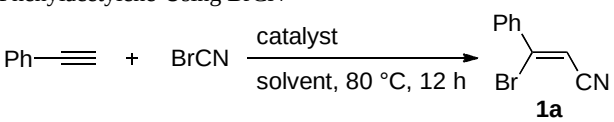
The catalytic addition reactions of X-Y-type substrates to carbon-carbon multiple bonds are of continued interest due to the facile access to 1,2-difunctional units from simple alkenes or alkynes with ideal atom efficiency.[1] Among these transformations, addition reactions of X-CN to alkynes simultaneously form vinyl-X and vinyl-carbon bonds, both of which can be used to construct complex structures. Several notable examples of palladium- or nickel-catalysed regio- and stereoselective addition reactions to alkynes with several X-CN groups have been reported, such as X=*H* (hydrocyanation),[2] X=*C* (carbocyanation),[3] X=*Si* (cyanosilylation),[4] X=*Ge* (cyanogermylation),[5] X=*Sn* (cyanostannylation),[6] X=*B* (cyanoboration),[7] X=*S* (cyanothiolation).[8] However, much less attention has been paid to catalytic regio- and stereoselective halocyanation of alkynes[9] or alkenes[10] using cyanogen halides. Herein, we report on gallium-catalysed bromocyanation of alkynes with cyanogen bromide, providing an efficient route to (*Z*)-β-bromoacrylonitriles in a high regio- and stereoselective fashion (Scheme 1). Taking advantage of (*Z*)-β-bromoacrylo- nitriles, we can establish efficient routes to a wide range of α,β-unsaturated nitriles,[11] which are of synthetic value.



Scheme 1 Catalytic Addition Reactions of X-CN to Alkynes.

When we examined the reaction of cyanogen bromide[12] and phenylacetylene using palladium or nickel/phosphine complexes, which are effective catalysts in addition reactions of X-CN to acetylenes (vide supra), no adducts were generated. Next, Lewis acids were screened for bromocyanation of alkynes, because there is a precedent for the haloacylation of alkynes in analogous reactions.[13] Representative results of the reaction of cyanogen bromide with phenylacetylene are shown in Table 1. We found that phenylacetylene underwent bromocyanation in the presence of $AlCl_3$ (10 mol%) in 1,2-dichloroethane at 80 °C to give β-bromocinnamonitrile **1a** in 42% yield as a mixture of *Z*- and *E*-isomers (*Z*:*E* = 89:11) (Table 1, entry 1). Interestingly, the use of $GaCl_3$ (10 mol%) instead of $AlCl_3$ led to **1a** in a high yield and stereoselectivity (81% chemical yield, *Z*:*E* = 92:8) (entry 2).[14] This is in sharp contrast with the non-catalysed bromocyanation of ynamines, which gave a low stereoselectivity of the adducts (*Z*:*E* = 50:50, ~ 60:40).[9a] The reaction using $GaCl_3$ at 70 °C led to a lower yield of **1a**, but with similar stereoselectivity (entry 3). 1,2-Dichloroethane was the most suitable solvent for bromo-cyanation, while other solvents, e.g., $CHCl_3$, toluene, heptane, and 2-methyltetrahydrofuran gave a lower yield of the adducts (entries 4-6), or no adducts (entry 7).[15] Using $GaBr_3$ as a catalyst afforded almost the same result as $GaCl_3$ (entry 8). Other Lewis acid catalysts, such as $InCl_3$ and $InBr_3$, showed marginal catalytic activity and gave lower yields of **1a** (entries 9 and 10), while $FeBr_3$, $CuBr_2$, and $ZnBr_2$ exhibited no catalytic activity for bromocyanation (entries 11-13). It should be noted that

Table 1. Lewis Acid-catalysed Bromocyanation of Phenylacetylene Using BrCN[a]



1a

entry	catalyst	solvent	yield[b]	*Z* : *E*[c]
1	$AlCl_3$	$ClCH_2CH_2Cl$	42%	89 : 11
2	$GaCl_3$	$ClCH_2CH_2Cl$	81% (72%)	92 : 8
3[d]	$GaCl_3$	$ClCH_2CH_2Cl$	41%	91 : 9
4	$GaCl_3$	$CHCl_3$	62%	90 : 10
5	$GaCl_3$	toluene	61%	90 : 10
6	$GaCl_3$	heptane	25%	91 : 9
7	$GaCl_3$	2-MeTHF	0%	——
8	$GaBr_3$	$ClCH_2CH_2Cl$	75%	96 : 4
9	$InCl_3$	$ClCH_2CH_2Cl$	15%	93 : 7
10	$InBr_3$	$ClCH_2CH_2Cl$	32%	95 : 5
11	$FeBr_3$	$ClCH_2CH_2Cl$	0%	——
12	$CuBr_2$	$ClCH_2CH_2Cl$	0%	——
13	$ZnBr_2$	$ClCH_2CH_2Cl$	0%	——

[a] Reaction conditions: Phenylacetylene (0.48 mmol) and BrCN (0.40 mmol) in solvent (1.6 mL) were heated in the presence of catalyst (10 mol%). [b] NMR yield (anisole as an internal standard). Isolated yield in parentheses. [c] Determined by NMR. [d] At 70 °C.

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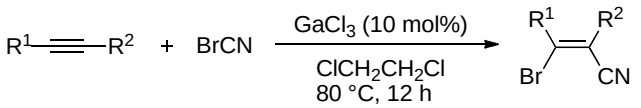
no chlorocyanation adducts were obtained even when Lewis acid catalysts bearing chloride ligands were used (entries 1-7 and 9).

With the optimized reaction conditions established (10 mol% $GaCl_3$ in 1,2-dichloroethane at 80 °C), we then examined the substrate scope of alkynes (Table 2). Arylacetylenes having a range of aromatic rings underwent bromocyanation of the alkyne moieties to give the corresponding (*Z*)-adducts, **1b-h**[16] in good yields with high regio- and stereoselectivity (entries 1-7), while 1-octyne and 1-(trimethylsilyl)acetylene gave no adducts. Reactions with internal aliphatic or alicyclic alkynes, such as 4-octyne and cyclooctyne, gave complex mixtures, while internal alkynes substituted by a phenyl ring produced bromocyanation adducts **1i**[17] and **1j**, having a cyano group at the β position to the phenyl group in good yields with high regio- and stereoselectivities (entries 8 and 9). Although the reaction of diphenylacetylene was sluggish, and required an elevated temperature (100 °C), the corresponding bromocyanation adduct **1k** was obtained in a 56% yield with excellent stereoselectivity (entry 10).

Table 2. $GaCl_3$-catalysed Bromocyanation of Alkynes Using BrCN[a]

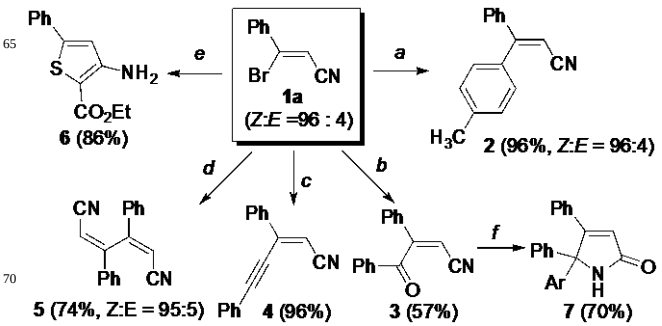


entry	R^1	R^2	product	isolated yield	$Z:E$[b]
1	4-$CH_3C_6H_4$	H	**1b**	70%	95 : 5
2	2-$CH_3C_6H_4$	H	**1c**	61%	98 : 2
3	2-naph	H	**1d**	55%	95 : 5
4	4-FC_6H_4	H	**1e**	71%	91 : 9
5	4-ClC_6H_4	H	**1f**	68%	90 : 10
6	4-BrC_6H_4	H	**1g**	68%	91 : 9
7	4-$CF_3C_6H_4$	H	**1h**	20%	92 : 8
8	Ph	CH_3	**1i**	70%	95 : 5
9	Ph	*n*-Bu	**1j**	72%	91 : 9
10[c]	Ph	Ph	**1k**	56%	99 : 1

[a] Reaction conditions: Alkynes (0.48 mmol) and BrCN (0.40 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) were heated in the presence of $GaCl_3$ (10 mol%). [b] Determined by NMR. [c] Reaction carried out in toluene at 100 °C.

The alkynophilicity[18] of trivalent GaX_3 leading to the formation of cationic vinylgallium species is well known, and some notable synthetic applications have been demonstrated.[19] To gain insight into the present bromocyanation of alkynes, we carried out an NMR study on a stoichiometric reaction. When $GaCl_3$ was added to a solution of BrCN in $CDCl_3$ at room temperature, the signal of CN (δ 76.1 ppm) in BrCN shifted to a new peak at δ 88.2 ppm. The downfield shift of the CN peak suggested the possibility of the formation of a complex between BrCN and $GaCl_3$.[20] When an equimolar amount of 1-phenyl-1-hexyne was added to a $CDCl_3$ solution of this complex at room temperature, the quantitative formation of the bromocyanation product **1j** (*Z*:*E* = 98:2) coordinated with $GaCl_3$ was observed, with the signal of the CN moiety being observed at δ 149.5 ppm. This result clearly shows that electrophilic addition of the BrCN and $GaCl_3$ complexes to alkynes[21] occurs, even at room temperature, and a high temperature is required in the catalytic reaction conditions to release $GaCl_3$ from cyano moiety of the adduct.

The synthetic utility of (*Z*)-β-bromo-α,β-unsaturated nitriles obtained from the bromocyanation of alkynes was demonstrated by the cross-coupling reactions of the representative product **1a** (Scheme 2). The Stille coupling reactions of **1a** with organostannanes afforded the stereo-defined structures **2** or **3** in good yields. The Sonogashira coupling reaction of **1a** with phenylacetylene gave enyne **4** quantitatively, with complete stereoselectivity. The nickel-catalysed reductive homo-coupling of **1a** produced 3,4-diphenyl-2,4-hexadiene-1,6-dinitrile **5**.[22] Moreover, we demonstrated the synthetic utility of **1a** and its derivative **3** in the preparation of the biologically active heterocycles **6**[23] and **7**.[11]



(a) $(4\text{-}CH_3C_6H_4)SnBu_3$, $Pd(PPh_3)_4$, CuI, dioxane, 100 °C, 8h. (b) $BzSnBu_3$, $Pd(OAc)_2$, PPh_3, dioxane, 100 °C, 12 h. (c) Phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, THF, rt, 5 h. (d) $NiBr_2(PPh_3)_2$, PPh_3, Zn, dioxane, 80 °C, 6 h. (e) Ethyl thioglycolate, NaOEt, EtOH, 70 °C, 12 h. (f) 1,3-Dimethoxybenzene, $Cu(OTf)_2$, $ClCH_2CH_2Cl$, H_2O, 80 °C, 15 h. Ar = $2,4\text{-}(MeO)_2C_6H_3$

Scheme 2 Transformation of **1a**.

In summary, we developed gallium(III)-catalysed bromocyanation of alkynes using cyanogen bromide. This method enables the regio- and stereoselective introduction of the synthetically useful Br and cyano functionalities to carbon-carbon triple bonds in single operation. Further investigations into the reaction mechanism, substrate scope, and the synthetic application are currently underway in our laboratory.

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16 The structure of the major stereoisomer of **1e** was unambiguously determined by X-ray crystallography. See electonic supplementary information for the detail of X-ray crystal analysis data. CCDC-796829 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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